

PCT/GB 00/00281

22 Feb 2000

09/8/00 721

REC'D 1 / MAR 2000

WIPO PCT

IA 201893

# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 03, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/120,326

FILING DATE: February 17, 1999

## PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN  
COMPLIANCE WITH RULE 17 1(a) OR (b)



By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS

  
T. WALLACE  
Certifying Officer

## PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

		Docket Number	39-172	Type a plus sign (+) inside this box-->	+
INVENTOR(S)/APPLICANT(S)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
POMFRETT ALKIRE HALER FALLON	Christopher Michael Richard Jim	J.D.	Cheshire CW11 0XQ, United Kingdom Costa Mesa, California 92626 Irvine, California 92612 Irvine, California 92612 · · · · ·		
TITLE OF THE INVENTION (280 characters)					
BRAIN METABOLISM					
CORRESPONDENCE ADDRESS					
Mary J. Wilson NIXON & VANDERHYE P.C. 1100 North Glebe Road 8 <sup>th</sup> Floor Arlington					
STATE	Virginia	ZIP CODE	22201	COUNTRY	U.S.A.
ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification	Number of Pages	12	<input type="checkbox"/>	Small Entity Statement	
<input type="checkbox"/> Drawing(s)	Number of Sheets	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Other (specify)	3 pages of claims (25)
METHOD OF PAYMENT (check one)					
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees (\$150.00)/(\$75)			PROVISIONAL FILING FEE AMOUNT (\$)	150.00	
<input checked="" type="checkbox"/> The commissioner is hereby authorized to charge filing fees and credit Deposit Account Number	14-1140				

The invention was made by an agency of the United States Government or under a contact with an agency of the United States Government.

No.  
 Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Mary J. Wilson

DATE

February 17, 1999

TYPED or PRINTED NAME

Mary J. Wilson

REGISTRATION NO.  
(if appropriate)

32,955

 Additional inventors are being named on separately numbered sheets attached hereto.

## PROVISIONAL APPLICATION FILING ONLY

Burden Hour Statement: This form is estimated to take .2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Office of Assistance Quality and Enhancement Division, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0651-0037), Washington, DC 20503. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

# ***U.S. PATENT APPLICATION***

*Inventor(s):* Christopher J.D. POMFRETT  
Michael ALKIRE  
Richard HALER  
Jim FALLON

*Invention:* BRAIN METABOLISM

*NIXON & VANDERHYE P.C.  
ATTORNEYS AT LAW  
1100 NORTH GLEBE ROAD  
8<sup>TH</sup> FLOOR  
ARLINGTON, VIRGINIA 22201-4714  
(703) 816-4000  
Facsimile (703) 816-4100*

## ***SPECIFICATION***

## BRAIN METABOLISM

The present invention relates to brain metabolism and more particularly to the regulation and monitoring of such metabolism. The invention relates particularly, but not exclusively, to regulation of brain metabolism to induce anaesthesia.

The level of brain metabolism is important in several physiological and pathological situations. For instance, during epilepsy brain metabolism tends to be inappropriately high (relative to a normal conscious subject) whereas during sleep (with the exception of Rapid Eye Movement sleep) or during hibernation brain metabolism tends to be less than in a conscious subject.

It is desirable to regulate brain metabolism in various circumstances. A reduction in brain metabolism is desirable in a variety of medical conditions or situations. For instance, a reduction in brain metabolism during an epileptic fit will promote recovery from the seizure. It is also desirable to increase brain metabolism in other medical conditions or situations. For example, an increase in brain metabolism will improve the alertness of an individual.

It is particularly important to be able to regulate brain metabolism when a clinician wishes to induce anaesthesia.

Small, volatile molecules which regulate brain metabolism and induce anaesthesia (e.g. alcohol's, halothane, ether, propofol etc) have been known for many years. However these conventional anaesthetics have various disadvantages including:

- (1) narrow concentration range over which the agent is effective (too little and the subject regains consciousness whereas too much results in coma or death);
- (2) slow recovery following anaesthesia; and
- (3) side effects (e.g. vomiting) induced by the anaesthetic agent.

The first and second aspects of the present invention seek to provide for regulation of brain metabolism (e.g. for the purposes of anaesthesia) whereas the third aspect of the present invention seeks to provide a method of evaluating brain metabolism.

According to a first aspect of the present invention, there is provided the use of a compound which mimics or modulates Delta-Sleep Inducing Peptide activity for the manufacture of a medicament for regulating brain metabolism.

By "brain metabolism" we mean energy metabolism in the brain. A low level of brain metabolism indicates that there is low energy utilisation (e.g. the state of the brain during a coma). High brain metabolism indicates there is high energy utilisation (e.g. during a brain seizure).

Delta-Sleep Inducing Peptide (DSIP) is known to induce sleep in mammals. It is a nonapeptide with the amino acid sequence:

Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu

We have found that compounds which mimic or modulate DSIP activity not only regulate sleep but are also able to regulate brain metabolism such that these compounds are useful in the regulation of a variety of medical situations. For instance, the compounds are useful for regulating sedation or epilepsy and are particularly useful for regulating brain metabolism when a clinician wishes to induce anaesthesia.

The invention is based upon our recognition that DSIP is an endogenous "anaesthetic-like" substance which modulates neurotransmission and brain metabolism. We have established that DSIP:

(1) regulates the balance between excitation and inhibition within the central nervous system (if excitation is too great, animals will undergo seizures whereas if inhibition is too great, animals become lethargic); and/or

(2) regulates arousal, sleep and hibernation (e.g. a decrease in brain energy utilisation during sleep and hibernation conserves energy).

Although we do not wish to be bound by any hypothesis, we believe that compounds which modulate DSIP activity are effective because they regulate binding of ligands with a neuromodulatory binding site on neuroreceptors (such as the site described by Mihic *et al.* (1997) *Nature* 389 p385-389 on GABA<sub>A</sub> receptors and glycine receptors). We believe binding of DSIP to these types of receptors modulates signalling mediated by these receptors and thereby regulates the level of brain metabolism.

According to a first embodiment of the first aspect of the invention compounds may be used which mimic or modulate DSIP such that DSIP activity is increased

Compounds according to the first embodiment of the first aspect of the invention may be used for reducing brain metabolism and may be used:

- (1) to induce sedation;
- (2) as an anticonvulsant (e.g. for treating epilepsy);
- (3) for inducing anaesthesia;
- (4) for enhancing anaesthetic activity;
- (5) for inducing analgesia;
- (6) as an anxiolytic;
- (7) as a premedicant to subsequent anaesthesia; and
- (8) as a neuroprotective following trauma.

We have also found that DSIP is associated with heart beat control and that reduced levels of DSIP results in an abnormal heart beat. It has been observed that DSIP modulates the level of Respiratory Sinus Arrhythmia (RSA). It has been suggested that abnormal levels of RSA are associated with subsequent Sudden Infant

Death Syndrome (SIDS). Therefore compounds may be used according to the first embodiment of the first aspect of the invention to reduce any predisposition to SIDS.

It has been observed that levels of DSIP are disturbed during Fatal Familial Insomnia (FFI). As DSIP is known to induce sleep we suggest that compounds according to the first embodiment of the first aspect of the invention may be used to treat patients exhibiting the symptoms of advanced FFI and also as a prophylactic treatment for patients genetically predisposed to develop the symptoms of FFI.

We have also found that compounds according the first embodiment of the first aspect of the invention may be used post myocardial infarction to regularise heart beat.

Several classes of compound which are capable of increasing DSIP activity may be used according to the invention. Such compounds include agonists or partial agonists of DSIP neuromodulatory binding sites, agents which enhance the release of endogenous agonists of DSIP neuromodulatory binding sites, agents which enhance the synthesis of endogenous agonists of DSIP neuromodulatory binding sites, agents which attenuate the breakdown (or removal from the synapse) of endogenous DSIP agonists, agents which increase DSIP expression or activity and agents which enhance the mechanisms involved in signal transduction between the ligand bound DSIP binding site and effector systems.

Preferred compounds which increase DSIP activity are DSIP agonists.

DSIP and pharmaceutically acceptable salts thereof may be used according to the first embodiment of the first aspect of the invention.

Biologically active fragments of DSIP, biologically active DSIP derivatives and larger peptides comprising the nonapeptide (or biologically active fragments and

derivatives thereof) are also preferred compounds for use according to the first embodiment of the first aspect of the invention.

It is particularly preferred that phosphorylated analogues of DSIP are used (such as the DSIP analogues disclosed in GB 2 000 511).

It will be appreciated that non-peptide compounds that mimic peptide DSIP agonist activity (which may be isolated from nature or rationally designed) may also be used.

Compounds which modulate DSIP activity are particularly useful in anaesthesia and may be used in a method of inducing anaesthesia comprising administering to a patient to be anaesthetised an amount of DSIP or a compound which promotes DSIP activity to induce at least part of the desired level of anaesthesia.

It is most preferred that the compounds are used as an adjunct to an anaesthetic. The compounds and the anaesthetic may be used in combination, simultaneously or sequentially. Use of the compound as an adjunct has the advantage of prolonging the time of action of the anaesthetic. It may also reduce the amount of anaesthetic required and thereby reduce the side-effects associated with the anaesthetic.

Our recognition that DSIP was an anaesthetic-sparing substance was based upon the following observations:

- (1) It is a neuromodulator, not necessarily a neurotransmitter, which influences the GABA<sub>A</sub> receptor in a manner consistent with a modulator working via the same site as the ethanol site and hence the enflurane anaesthetic site.
- (2) It is an anticonvulsant.

(3) It has analgesic properties, and thus should be MAC sparing (MAC being the Minimum Alveolar Concentration of anaesthetic necessary to achieve loss of movement to a noxious stimulus in 50% of subjects). We believe DSIP is analgesic because it promotes the release of met-enkephalin.

(4) It is involved with loss of consciousness and promotes delta wave activity on the electroencephalograph as do many anaesthetics.

(5) It may modulate general levels of excitation and inhibition within the brain. It is known to inhibit thermoregulation, as do general anaesthetics.

We subsequently confirmed our hypothesis that DSIP may act as an anaesthetic, and particularly an anaesthetic sparing agent, by experiments which established that administration of DSIP induces anaesthesia and also prolongs anaesthesia induced by other anaesthetic agents. For instance, anaesthesia following a 7mg/kg iv bolus of propofol is approximately 28% longer in animals pre-treated with DSIP (1mg/kg i.v. 15 mins prior to the propofol bolus) compared to animals treated with propofol alone.

Furthermore, compounds which promote DSIP activity allow for instantaneous reversal, or at least quicker reversal, of general anaesthesia thereby improving or eliminating anaesthetic recovery times and improving anaesthetic safety.

Induction of anaesthesia is frequently associated with undesirable side effects such as respiratory depression whereby the patient stops spontaneous breathing.

Administration of DSIP is not associated with respiratory depression therefore, by administering a combination of DSIP with lower dose anaesthesia, induction of anaesthesia will be achieved without respiratory depression.

Compounds used according to the first embodiment of the first aspect of the invention are also useful as a sedative or premedicant which may be administered to a subject before full anaesthesia is to be induced.

According to a second embodiment of the first aspect of the invention compounds may be used to modulate DSIP such that DSIP activity is decreased.

Compounds according to the second embodiment of the first aspect of the invention may be used for increasing brain metabolism and may be used:

- (1) to increase alertness in a subject; and
- (2) for promoting recovery from anaesthesia.

Several classes of compound which are capable of decreasing DSIP activity may be used according to the second embodiment of the first aspect of the invention. Such compounds include antagonists or partial agonists of DSIP neuromodulatory binding sites, agents which inhibit the release of endogenous agonists of DSIP neuromodulatory binding sites, agents which inhibit the synthesis of endogenous agonists of DSIP neuromodulatory binding sites, agents which promote the breakdown (or removal from the synapse) of endogenous DSIP agonists, agents which decrease DSIP expression or activity and agents which inhibit the mechanisms involved in signal transduction between the ligand bound DSIP binding site and effector systems.

Preferred compounds which decrease DSIP activity are DSIP antagonists and include melatonin, dalargin and neokyotorphin.

We have found that a decrease in levels of DSIP increases alertness of a subject. Thus anti-DSIP drugs may be used to reverse feelings of drowsiness (e.g. to keep a pilot or long distance driver alert).

A preferred use of compounds which decrease DSIP activity is to promote recovery from anaesthesia. Thus, immediately before an operation, compounds according to the first embodiment of the first aspect of the invention may be used to anaesthetise or assist in anaesthetising a subject and then, once the procedure has been completed, compounds according to the second embodiment of the first aspect of the invention may be used to expedite recovery from anaesthesia.

The compounds according to the first or second embodiments of the first aspect of the invention may be used when prophylactic treatment is considered medically necessary. For instance, according to the first embodiment of the first aspect of the invention an epileptic may be given a DSIP agonist or DSIP itself to prevent the development of seizures and control a patient in seizure. Alternatively a security guard, driver or pilot may use a DSIP antagonist according to the second embodiment of the first aspect of the invention to increase alertness (especially before working at night or for prolonged hours).

Brain metabolism may be regulated with compounds which modulate DSIP activity either as a monotherapy or in combination with other agents. For instance, anaesthesia may be induced with compounds according to the first embodiment of the first aspect of the invention alone (a monotherapy) or in combination with other known anaesthetic agents (e.g. combination therapy with a DSIP agonist as an anaesthetic cofactor for propofol).

When the compounds are used in combination with other agents, a lower dose of that agent may be required. This will reduce the incidence and severity of side-effects known to be caused by such agents.

The compounds used according to the invention may take a number of different forms depending, in particular on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet,

capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle of the composition of the invention should be one which is well tolerated by the subject to whom it is given and enables delivery of the compounds to the target tissue.

The compounds may be used in a number of ways. For instance, systemic administration may be required in which case the compound may be contained within a composition which may for example be ingested orally in the form of a tablet, capsule or liquid. Alternatively the compound may be administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion). The compounds may also be administered by inhalation. Alternatively the compounds may be administered to a pregnant female to be conveyed via the placenta for treatment of the fetus or to a female to deliver the compound to a neonate in her milk.

Compounds modulating DSIP activity may be administered centrally by means of intracerebral, intracerebroventricular, or intrathecal delivery.

The compound may also be incorporated within a slow or delayed release device. Such devices may, for example, be inserted under the skin and the compound may be released over weeks or even months for the regulation of brain metabolism. This may be particularly advantageous when a compound is used which would normally require frequent administration (e.g. at least daily injection). Such devices are useful in the long term prophylactic treatment of epileptics or to help insomniacs.

It will be appreciated that the amount of a compound required is determined by biological activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the compound employed and whether the compound is being used as a monotherapy or in a combined therapy. The

capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle of the composition of the invention should be one which is well tolerated by the subject to whom it is given and enables delivery of the compounds to the target tissue.

The compounds may be used in a number of ways. For instance, systemic administration may be required in which case the compound may be contained within a composition which may for example be ingested orally in the form of a tablet, capsule or liquid. Alternatively the compound may be administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion). The compounds may also be administered by inhalation. Alternatively the compounds may be administered to a pregnant female to be conveyed via the placenta for treatment of the fetus or to a female to deliver the compound to a neonate in her milk.

Compounds modulating DSIP activity may be administered centrally by means of intracerebral, intracerebroventricular, or intrathecal delivery.

The compound may also be incorporated within a slow or delayed release device. Such devices may, for example, be inserted under the skin and the compound may be released over weeks or even months for the regulation of brain metabolism. This may be particularly advantageous when a compound is used which would normally require frequent administration (e.g. at least daily injection). Such devices are useful in the long term prophylactic treatment of epileptics or to help insomniacs.

It will be appreciated that the amount of a compound required is determined by biological activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the compound employed and whether the compound is being used as a monotherapy or in a combined therapy. The

frequency of administration will also be influenced by the above mentioned factors and particularly the half-life of the compound within the subject being treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials etc), may be used to establish specific formulations of compositions and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration).

Generally, a daily dose of between 0.01 µg/kg of body weight and 1.0 g/kg of body weight of a compound which modulates DSIP activity may be used for the regulation of brain activity depending upon which specific compound is used and the reason for regulating activity. For instance, a suitable dose of a DSIP agonist will be in the range of between 1.0 µg/kg/day and 1.0 g/kg/day. Purely by way of example a suitable dose of DSIP for use in combination with propofol (e.g. 7mg/kg IV bolus) for inducing anaesthesia is between 0.01mg and 100 mg/kg and preferably between 0.02 mg/kg and 10 mg/kg. By way of further example a daily dose of DSIP suitable for prophylactic treatment of epilepsy is between 1 µg/kg and 10 mg/kg and preferably about 1 mg/kg.

Daily doses may be given as a single administration (e.g. a single daily injection). Alternatively the compound used may require administration twice or more times during a day or even continuous administration (such as may be required during anaesthesia).

According to a second aspect of the present invention, there is provided a method of regulating brain metabolism comprising administering to a subject a compound which modulates Delta-Sleep Inducing Peptide activity.

The compounds which modulate DSIP activity and conditions requiring regulation of brain metabolism according to the first aspect of the invention are applicable to the method of the second aspect of the invention.

The fact that neuroactive peptides, such as DSIP, play a role in regulating brain metabolism is physiologically and medically important and according to a third aspect of the present invention there is provided a method of evaluating the brain metabolism of a subject comprising assaying a sample taken from the subject for the presence of Delta-Sleep Inducing Peptide.

A suitable assay for measuring DSIP levels in a sample is a quantitative immunoassay method utilising antibodies raised against DSIP and/or a biosensor based on the binding site of DSIP.

The sample is most suitably a blood or urine sample. DSIP is also found in milk and may be assayed from milk samples.

According to a preferred embodiment of the method of the third aspect of the invention, we have found that anaesthetic dose requirements are directly related to endogenous levels of DSIP. Thus an assay of DSIP levels in a subject (e.g. a simple urine or blood test screening for DSIP) provides an anaesthetic dosage guide for predicting anaesthetic requirements. High endogenous levels of DSIP indicate lower anaesthetic requirements. Such a test may be used pre-operatively to evaluate the anaesthetic needs of elective surgical patients.

High measured levels of DSIP (and therefore low brain activity) may also be used to predict when people are at most risk of sleepiness and therefore may be liable to make mistakes. For instance, DSIP levels may be assayed for pilots before beginning night flight operations.

602720-32502100

DSIP levels may also be monitored to assess when people have adapted to unsociable shift patterns. When the brain has adapted to express lower DSIP levels during night time it delineates that shift workers (e.g. pilots flying nights) have best adapted to night schedules because lower DSIP levels indicate higher brain activity and correspond to higher alertness.

DSIP monitoring is also useful for evaluating whether or not a baby is likely to have a predisposition to SIDS.

Furthermore we propose that DSIP levels correlate with intelligence (and Intelligence Quotient; I.Q.), or psychomotor performance ability. Thus the method of the third aspect of the invention may be used to assess whether or not a person would be suited for a mentally demanding position (Low DSIP levels would suggest an aptitude).

Whole-brain baseline metabolic rate may correlate with DSIP levels. PET may be a non-invasive measure of regional DSIP activity. Therefore PET scanning may reveal which brain areas are important in regulating DSIP levels and we therefore feel that PET scanning is one way by which DSIP may be monitored.

CLAIMS

1. The use of a compound which mimics or modulates Delta-Sleep Inducing Peptide activity for the manufacture of a medicament for regulating brain metabolism.
2. The use according to claim 1, wherein Delta-Sleep Inducing Peptide activity is promoted.
3. The use according to claim 2, wherein brain metabolism is regulated such that anaesthetic activity is enhanced.
4. The use according to claim 3 wherein anaesthetic activity is enhanced in the operating theatre.
5. The use according to claim 2, wherein brain metabolism is regulated such that anaesthesia is promoted.
6. The use as claimed in claim 3-5 wherein the Delta-Sleep Inducing Peptide is used in conjunction with another anaesthetic agent.
7. The use according to claim 2, wherein brain metabolism is regulated such that sedation is induced.
8. The use according to claim 7 wherein sedation is induced in intensive care.
9. The use according to claim 2, wherein brain metabolism is regulated such that convulsions are inhibited or terminated.
10. The use according to claim 2 wherein the compound is used in the treatment or prophylactic treatment of Fatal Familial Insomnia.

654770-200000000000

11. The use according to claim 2 wherein the compound is used to regularise heart beat post myocardial infarction.

12. The use according to any one of claims 2-11, wherein the compound is Delta-Sleep Inducing Peptide or a biologically active fragment or derivative thereof.

13. The use according to claim 12 wherein the compound is a nonapeptide with the amino acid sequence:

Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu

- or biologically active fragments and derivatives thereof.

14. The use according to claim 13 wherein at least one amino acid or derivative thereof of the nonapeptide is phosphorylated.

15. The use according to any one of claims 2-11 wherein the compound is any one of an agonist or partial agonist of a DSIP neuromodulatory binding site, an agent which enhances the release of endogenous agonists of DSIP neuromodulatory binding sites, an agent which enhances the synthesis of endogenous agonists of DSIP neuromodulatory binding sites or an agent which attenuates the breakdown (or removal from the synapse) of endogenous DSIP agonists.

16. The use according to claim 1, wherein Delta-Sleep Inducing Peptide activity is inhibited.

17. The use according to claim 16, wherein brain metabolism is regulated such that alertness is increased in a subject.

18. The use according to claim 16, wherein brain metabolism is regulated such that recovery from anaesthesia is promoted.

PCT/GB2002/002659

19. A method of evaluating the brain metabolism of a subject comprising assaying a sample taken from the subject for the presence of Delta-Sleep Inducing Peptide.

20. The method according to claim 19, wherein the sample is a milk, blood or urine sample.

21. The method according to claim 19 or 20, wherein the measured brain metabolism predicts anaesthetic dosage requirements.

22. The method according to claim 19 or 20, wherein the measured brain metabolism predicts whether or not a person is feeling tired.

23. The method according to claim 19 or 20, wherein the measured brain metabolism predicts whether or not a person has adapted to shift patterns.

24. The method according to claim 19 or 20, wherein the measured brain metabolism predicts the Intelligence Quotient of a person.

25. The method according to claim 19 or 20, wherein the measured brain metabolism predicts whether or not a baby is predisposed to Sudden Infant Death Syndrome.

RECORDED BY  
DRAFTING, DESIGN  
AND DRAWING

